(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 July 2004 (08.07.2004)

PCT

(10) International Publication Number
WO 2004/056354 A1

(51) International Patent Classification[7]: A61K 31/18, 9/16, A61P 13/08

(21) International Application Number: PCT/IB2003/006072

(22) International Filing Date: 18 December 2003 (18.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1292/DEL/2002 20 December 2002 (20.12.2002) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, 110019 New Delhi, Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JAIN, Girish, Kumar** [IN/IN]; 4, Sharda Niketan, Teachers' Colony, Pitampura, 110 034 Delhi, Delhi (IN). **SRITHARAN, Seetharaman** [IN/IN]; - (IN). **RAMPAL, Ashok** [IN/IN]; 14, Sewa Nagar, Ram Tirath Road, 143001 Amritsar, Punjab (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TAMSULOSIN

(57) Abstract: The present invention relates to controlled release pharmaceutical compositions of tamsulosin or its pharmaceutically acceptable salts thereof. More particularly, the invention relates to a controlled release individual unit or multiple unit formulation comprising a spherical core obtained by adding release controlling agent to a mixture of tamsulosin and spheronizing agent.

WO 2004/056354 A1

CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS OF TAMSULOSIN

Field of the Invention

The technical field of the invention relates to controlled release pharmaceutical compositions of tamsulosin or pharmaceutically acceptable salts thereof. More particularly, the invention relates to a controlled release individual unit or multiple unit formulation comprising a spherical core obtained by adding a release controlling agent to a mixture of tamsulosin and a spheronizing agent. The invention also relates to methods of preparing such formulations.

Background of the Invention

The need to improve the clinical results of modified release formulations is well documented in the prior art. This is particularly important for drugs that have short half-lives, region specific absorption, produce gastric irritation, or have other side effects at high plasma concentrations. One of the most common methods of achieving modified drug release involves the use of monolithic systems designed to have modified release characteristics. These monolithic systems vary from osmotic drug delivery systems to bioerodible or non-erodible matrix based systems.

Although a major portion of the modified release formulations currently prescribed are monolithic systems, they nonetheless suffer from a few serious drawbacks. Intentional or accidental breakdown of the delivery system is one of the limitations that may cause dose dumping. Dose dumping may lead to toxic or fatal effects, depending on the pharmaceutical compound. Further, the gastric emptying of the comparatively large monolithic systems is variable and is dependent on the presence or absence of food, as well as the type of food taken by the patient.

These disadvantages have prompted a shift in modified release technology from the use of monolithic systems to multiple unit systems, wherein each individual unit is formulated with modified release characteristics. The final dosage form consists of a collection of the multiple units, compressed into a tablet, or filled into a capsule or sachet. When administered, the individual units are dispersed freely into the gastrointestinal contents, avoiding the high local concentration of drug which may lead to irritation of gastrointestinal mucosa. Also, the performance of the dosage form is independent of inter-

and intra-patient variability in gastric emptying time because of the small size of the individual units that make up the system.

Multiple unit dosage forms possess large surface area, which promotes complete and uniform absorption, minimize peak plasma fluctuations and thus reduce the potential for systemic side effects. Further advantages of these dosage forms are that high local concentrations of the active substance in the gastrointestinal system is avoided, due to the units being distributed freely throughout the tract, less variation in absorption is observed and there is reproducibility in the dissolution characteristics.

Drug release from such extended release multiple units is controlled either by diffusion of a coating or by erosion of the coating by a process dependent on enzymes or pH. The erodible coatings involve the use of enteric polymers, which rapidly erode in the intestines.

There are a number of methods available for manufacturing these multiple units, which include:

(a) Extrusion-spheronization

(b) Wet granulation

(c) Dry granulation: There are two main processes for dry granulation:

1. Slugging
2. Roller compaction

Extrusion/spheronization is a multistep process used to make uniformly sized particles. It is used primarily to produce multiparticulates for controlled or sustained release applications. This process is also used to increase the bulk density, improve flow properties and reduces the problem of dust usually encountered with low-density, finely divided active and excipient powders. The general process involves separate processes of wet massing, followed by extrusion of this wet mass into cylindrical segments and subsequent spheronization of these segments to round off these cylindrical segments into spherical particles. Extrusion involves forcing the wet mass through dies and shaped into cylindrical particles with uniform diameter. The extrudate particles break at similar lengths. These particles are rounded off into spherical particles in an apparatus, which consists of a bowl with fixed sidewalls and rapidly rotating bottom plate or disc. The rounding off is dependent on frictional forces generated by particle-particle and particle-

equipment collisions. This process of rounding off constitutes spheronization. This process requires the incorporation of an agent that aids in the rounding off of the particles which is known as rounding or spheronizing agent.

Tamsulosin, 5–[(2R)–2–[[2–(2–ethoxy–phenoxy) ethyl] amino] propyl]-2-methoxy benzene sulfonamide, is an α_1-adrenoceptor blocking agent, exhibiting selectivity for α_1-receptors in the human prostate. It is disclosed in EP 34432 and U.S. Patent No. 4,731,478 as a pharmaceutically active substance having alpha-adrenergic blocking activity that is useful for treatment of cardiac insufficiencies and benign prostatic hyperplasia.

The pharmacokinetic studies of tamsulosin show that it is absorbed from the intestine and is almost completely bioavailable.

U.S. Patent No. 4,772,475 discloses an oral pharmaceutical controlled release multiple unit formulation in which the individual units comprise a granulation product of a release controlling agent, physiologically active substance and units-forming substance (s). The patent emphasizes that the unit-forming substance (crystalline cellulose) should at least be 50% by weight. The drug containing units of this invention have high mechanical strength and can control dissolution rate without enteric coating.

However, since tamsulosin is absorbed from the intestine, the object should be to develop a composition, which releases the drug gradually in the intestine where it is completely absorbed.

The inventors have now discovered that enteric-coated, controlled release formulation of tamsulosin provides release at the desired site. The controlled release formulation can be prepared with less than 50% w/w of a spheronizing agent.

Summary of the Invention

In one general aspect there is provided a controlled release pharmaceutical composition of tamsulosin that includes a spheroid core. The core includes tamsulosin, about 10% to about 45% w/w of a spheronizing agent and one or more rate controlling polymers; and an outer enteric coating layer. The enteric coating is placed over the core.

The core may include one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose. The sugar may include one or more of glucose, mannitol, lactose, xylitol,

dextrose, and sucrose. The core may include one or more of an insoluble material, a soluble material, and a swellable material.

Embodiments of the pharmaceutical composition are prepared by a spheronization process. The spheronizing agent may be microcrystalline cellulose. The tamsulosin may include one or more of free base, pharmaceutically acceptable salts and isomers of tamsulosin. The pharmaceutically acceptable salts of tamsulosin may be one or more of hydrochloride, hydroiodide, hydrobromide, hydrogen fumarate, and the like. For example, the pharmaceutically acceptable salt of tamsulosin may be hydrochloride. The pharmaceutical composition may contain a concentration of from about 0.03% to about 0.33% by weight of tamsulosin.

The rate controlling polymer may include one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof. The rate controlling polymer may be present in the pharmaceutical composition at a concentration of from about 20% to about 90% by weight.

The enteric polymer may include one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid, and ethyl acrylate copolymer. In particular, the enteric polymer may include one or more of methacrylic acid and ethyl acrylate copolymer.

The wax may include one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof. The wax may include one or more of glyceryl monostearate and stearic acid.

The water soluble polymer may include one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

The water insoluble polymer may include one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

The alkaline metal salts of higher fatty acid may include one or more of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof. In particular, the alkaline metal salt of higher fatty acid may include magnesium stearate.

The spheroid core may include one or more of pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of plasticizers, diluents, colorants and flavoring agents.

The enteric coating may include one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid and mixtures thereof. The enteric coating may also have one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

The pharmaceutical composition may be formulated into capsules, sachets, and tablets.

In another general aspect there is provided a process for the preparation of a controlled release pharmaceutical composition of tamsulosin. The process includes providing spherical cores that includes tamsulosin, a spheronizing agent and one or more of rate controlling polymers; and coating the spheroid cores with an enteric polymer. The core may be prepared by extrusion-spheronization. The extrusion-spheronization process may include granulating tamsulosin, spheronizing agent and one or more rate controlling polymers, extruding the granulated mixture to obtain extrudates, spheronizing the extrudates to obtain spherical cores, drying the spheroid cores; and coating the spheroid cores with an enteric polymer.

The tamsulosin may include one or more of free base, pharmaceutically acceptable salts and isomers of tamsulosin. The pharmaceutically acceptable salts of tamsulosin may be one or more of hydrochloride, hydroiodide, hydrobromide, hydrogen fumarate, and the like. In one embodiment, the pharmaceutically acceptable salt of tamsulosin may be hydrochloride. The pharmaceutical composition may contain a concentration of from about 0.03% to about 0.33% by weight of tamsulosin.

The rate controlling agent may include one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof at a concentration of from about 20% to about 90% by weight of the composition.

The enteric polymer may include one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid, and ethyl acrylate copolymer.

In particular, the enteric polymer may include one or more of methacrylic acid and ethyl acrylate copolymer.

The wax may include one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof. In particular, the wax may include one or more of glyceryl monostearate and stearic acid.

The water soluble polymers may include one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

The water insoluble polymers may include one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

The alkaline metal salts of higher fatty acid may include one or more of magnesium stearate, zinc stearate, calcium stearate and mixtures thereof. In particular, the alkaline metal salt of higher fatty acid may include magnesium stearate.

The spheroid core may include one or more of pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of plasticizers, diluents, colorants and flavoring agents.

The enteric coating may include one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid and mixtures thereof. The enteric coating may also have one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

The pharmaceutical composition may be formulated into capsules, sachets, and tablets.

In another general aspect there is provided a process for the preparation of a controlled release pharmaceutical composition of tamsulosin. The process includes granulating tamsulosin and spheronizing agent with dispersion of one or more of rate controlling polymers, extruding the granulates to form extrudates using an extruder, spheronizing the extrudates until spherical cores are formed; and coating the spheroid cores with an enteric polymer.

The tamsulosin may include one or more of free base, pharmaceutically acceptable salts and isomers of tamsulosin. The pharmaceutically acceptable salts of tamsulosin may be one or more of hydrochloride, hydroiodide, hydrobromide, hydrogen fumarate, and the like. In one embodiment, the pharmaceutically acceptable salt of

tamsulosin may be hydrochloride. The pharmaceutical composition may contain a concentration of from about 0.03% to about 0.33% by weight of tamsulosin.

The rate controlling agent may include one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof at a concentration of from about 20% to about 90% by weight of the composition.

The enteric polymer may include one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid, and ethyl acrylate copolymer. In particular, the enteric polymer may include one or more of methacrylic acid and ethyl acrylate copolymer.

The wax may include one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof. In particular, the wax may include one or more of glyceryl monostearate and stearic acid.

The water soluble polymers may include one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

The water insoluble polymers may include one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

The alkaline metal salts of higher fatty acid may include one or more of magnesium stearate, zinc stearate, calcium stearate and mixtures thereof. In particular, the alkaline metal salt of higher fatty acid may include magnesium stearate.

The spheroid core may include one or more of pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more of plasticizers, diluents, colorants and flavoring agents.

The enteric coating may include one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid and mixtures thereof. The enteric coating may also have one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

The pharmaceutical composition may be formulated into capsules, sachets, and tablets.

In another general aspect, a method for preparing a controlled release pharmaceutical composition includes providing a core having a coating, forming individual units, and forming the dosage form by combining one or more individual units.

Embodiments of the method of preparing a controlled release multiple unit dosage form may include one or more of the following features, including any one or more of the features described above. Combining one or more individual units may include filling the individual units into a capsule or sachet or compressing the individual units into a tablet.

In another general aspect there is provided a method of treating symptoms of benign prostatic hyperplasia. The method includes administering a controlled-release pharmaceutical composition of tamsulosin, which includes a spheroid core. This core includes tamsulosin, about 10% to about 45% w/w of a spheronizing agent, and one or more ratecontrolling polymers. The core is then coated by an enteric coating.

Embodiments of the method may contain any one or more features described above. The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The present invention relates to controlled release individual unit or multiple unit formulation comprising an enteric coated spherical core, wherein the core comprises tamsulosin, about 10% to about 45% w/w of a spheronizing agent and rate controlling polymers.

The term spheroid is conventional in the pharmaceutical art and means a spherical granule having a diameter of between about 0.1mm and 2.5mm.

Tamsulosin may comprise free base, pharmaceutically acceptable salts or isomers of tamsulosin thereof. The pharmaceutically acceptable salts may include hydrochloride, hydroiodide, hydrobromide, hydrogen fumarate, and the like. Tamsulosin constitutes about 0.03 to about 0.33% by weight of the formulation.

The spheronizing agent may comprise any pharmaceutically acceptable material, which may be spheronized together with the active ingredient to form spheroid cores. The

most commonly used spheronizing agent is microcrystalline cellulose. The microcrystalline cellulose employed may be, for example, Avicel® PH 101 or Avicel® PH 102 commercially available from FMC Corporation. The spheronizing agent may be present in an amount ranging from about 10% to about 45% by weight of the formulation.

The rate controlling agent may include one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof.

Suitable enteric polymers include those known in the art, such as hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, polymethylacrylates and copolymers of acrylic and methacrylic acid (commercially available under the trade name of Eudragit®), for example, Eudragit L30D-55 (anionic aqueous polymer dispersion of methacrylic acid – ethyl acrylate copolymer), Eudragit L100-55 (Spray-dried Eudragit L30D-55 which can be reconstituted as aqueous dispersion), Eudragit L100 (anionic polymer powder solubilizing above pH 6.0) and Eudragit S100 (anionic polymer powder solubilizing above pH 7.0).

Suitable waxes include one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids such as stearic acid and oleic acid, and mixtures thereof.

Suitable water-insoluble polymers include one or more of ethyl cellulose, cellulose acetate, copolymers of polyethylene and vinyl acetate, methacrylic acid methyl methacrylate copolymers with quaternary ammonium groups such as those sold under the trade name Eudragit® RL, Eudragit® RS and Eudragit® NE, and the like.

Suitable examples of the alkaline metal salts of a higher fatty acid include one or more of magnesium stearate, zinc stearate, calcium stearate, and the like.

Suitable water-soluble polymers may include one or more of polyvinylpyrrolidone, carboxymethylcellulose sodium, hydroxylpropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, methylcellulose, and mixtures thereof.

The rate controlling polymers may comprise about 20 to about 90% by weight of the formulation. The rate controlling polymers in accordance with this invention may also act as binder and may be added as such or dissolved or dispersed in an appropriate solvent system and the resulting solution or dispersion is then used to granulate the active agent. The resulting granulated mass may then be subjected to extrusion and spheronization.

This method of incorporation allows the rate controlling polymers to more effectively retard drug release.

Optionally, in addition to the active ingredient, spheronizing agent and rate controlling polymers, the spheroid cores may also contain other pharmaceutically acceptable excipients. The other pharmaceutically acceptable excipients as used herein include plasticizers, diluents, colorants, and flavoring agents.

Suitable diluents include one or more of lactose, starch, sugar alcohols, sucrose and mixtures thereof.

The controlled release composition according to this invention may be prepared by:

a. granulating tamsulosin, spheronizing agent and rate controlling polymers with water,

b. extruding the granulated mixture to give extrudates; and

c. spheronizing the extrudates until spherical cores are formed.

Alternatively, granulation according to step a) may be carried out with a dispersion of rate controlling polymers.

Extrusion may be carried out in any of the extruders such as screw-feed extruders and gravity-feed extruders such as cylindrical roll or gear roll and piston-feed extruders.

The pharmaceutical composition according to the present invention further includes an enteric coating over the spheroid core. This coating will substantially eliminate dissolution in the acidic environment of the stomach but will dissolve sufficiently to permit release in a controlled manner over an extended period in the intestine.

Examples of enteric coatings include one or more of neutralized hydroxypropyl methylcellulose phthalate (HPMCP) coating, beeswax, glyceryl monostearate, shellac and cellulose, shellac and stearic acid; neutral copolymer of methacrylic acid and methacrylic acid methyl ester (Eudragit®) or a neutral copolymer of polymethacrylic acid esters containing metallic stearates.

The other enteric coating polymers known in the art may also be employed, including one or more of polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate succinate and the like.

Most of the enteric coating materials are acidic in nature and hence may cause chemical instability when in contact with active ingredient. However, this can be avoided by using suitable alkalizing agents like sodium hydroxide, potassium hydroxide, calcium carbonate, sodium carboxymethylcellulose, magnesium oxide and magnesium hydroxide. The enteric coating may also contain a plasticizer, which may be one or more of citrate, triacetin, diethyl phthalate, dibutyl phthalate, polyethylene glycol, propylene glycol, glycerol, tributyl citrate, and the like. The enteric coating may also include anti-adherent or tack-modifiers as an inert aid in the stability of coating process. Suitable tack-modifier may include one or more of talc, kaolin or colloidal anhydrous silica. The coating may also include an opacifier such as titanium dioxide.

The enteric coating layer can be formed on the surface of the spheroid cores, using conventional coating methods, such as fluidized or pan coating.

The compositions prepared according to the invention may be filled into capsules, sachets or compressed into tablets using conventional pharmaceutical techniques.

The improved, multiple unit systems described above are further illustrated by the following examples. Although these examples are illustrative of the techniques, compositions, and concepts described herein, they are not intended to be limiting.

EXAMPLE 1

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	126
	Magnesium stearate	20
	Starch	64.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	79.0
	Purified water	q.s.
Enteric coat	Methacrylic acid ethyl acrylate copolymer	6.59
	Sodium hydroxide	0.08
	Triacetin	0.99
	Talc	1.31
	Titanium dioxide	0.11
	Purified water	q.s

EXAMPLE 2

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	126
	Glyceryl mono stearate	20
	Starch	64.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	79.0
	Purified water	Qs
Enteric coat	Same as for example 1	

EXAMPLE 3

	Ingredients	Mg/capsule
Core	Tamsulosin hydrochloride	0.4
	Microcrystalline cellulose	118
	Stearic acid	18
	Starch	60.6
	Methacrylic acid-ethyl acrylate copolymer dispersion	74
	Povidone	5
	Purified water	Qs
Enteric coat	Same as for Example 1	

Process:

1. Tamsulosin hydrochloride is dissolved in water and the solution is used to granulate microcrystalline cellulose, in a mixer.
2. Granulate of step 1 is dried in a fluidized bed dryer at 60°C and sieved to a particle size of less than about 600 μ.
3. Magnesium stearate/ glyceryl mono stearate/ stearic acid and starch are sieved to a particle size of less than about 600 μ and mixed with granulate of step 2 in a mixer.
4. The blend of step 3 is granulated with the dispersion of methacrylic acid-ethyl acrylate copolymer (Eudragit L30D 55) in a rotary mixer grinder. In Example 3, same blend is further granulated by 10% solution of povidone in water.
5. Granulate of Step 4 is extruded through a bore of inner diameter of 1mm.
6. The extrudates of step 5 are spheronized-using spheronizer fitted with plate of 3.25 mm pitch.
7. Spherical cores obtained in step 6 are dried in fluidized bed dryer at 60°C for one hour.

8. Enteric coating dispersion of Eudragit L100: 55 is prepared by dispersing enteric coating materials in water.

9. The spherical cores of step 7 are coated with the dispersion of step 8, to a weight gain of about 3.33% w/w.

10. The coated cores of step 9 are filled in capsules.

The resulting capsules of Example 1 were compared with FLOMAX capsules (containing 0.4mg tamsulosin marketed by Boehringer Ingelheim) for in vitro release of tamsulosin. The dissolution studies were performed using USP Apparatus II at 50 rpm in 500ml phosphate buffer pH 6.8. The results are shown in Table 1.

Table 1: Comparative in vitro release data of tamsulosin from capsules (of Example 1) and FLOMAX capsules (of Boehringer Ingelheim) using USP dissolution apparatus II/ 500 ml/ pH 6.8 phosphate buffer/ 50 rpm

Time (hrs)	Percent tamsulosin released (%)	
	from Capsules of Example 1	from FLOMAX capsules
1	45	39
2	71	61
4	90	90
6	94	107

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

WE CLAIM:

1. A controlled release pharmaceutical composition of tamsulosin, the composition comprising:

(a) a spheroid core comprising:

i. tamsulosin,

ii. about 10% to about 45% w/w of a spheronizing agent,

iii. one or more of rate controlling polymers, and;

(b) an enteric coating over the spheroid core.

2. The composition of claim 1, wherein the tamsulosin comprises free base, pharmaceutically acceptable salts and isomers of tamsulosin.

3. The composition of claim 2, wherein the pharmaceutically acceptable salts of tamsulosin comprise one or more of hydrochloride, hydroiodide, hydrobromide, and hydrogen fumarate..

4. The composition of claim 3, wherein the pharmaceutically acceptable salt of tamsulosin is a hydrochloride.

5. The composition of claim 1, wherein the composition comprises a concentration from about 0.03% to about 0.33% by weight of tamsulosin.

6. The composition of claim 1, wherein the spheronizing agent is microcrystalline cellulose.

7. The composition of claim 1, wherein the rate controlling polymer comprises one or more of enteric polymers, water insoluble polymers, water soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof.

8. The composition of claim 1, wherein the composition comprises from about 20% to about 90% by weight of rate controlling polymers.

9. The composition of claim 7, wherein the enteric polymer comprises one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid and ethyl acrylate copolymer.

10. The composition of claim 9, wherein the enteric polymer comprises one or more of methacrylic acid and ethyl acrylate copolymer.

11. The composition of claim 7, wherein the wax comprises one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof.

12. The composition of claim 11, wherein the wax is glyceryl monostearate.

13. The composition according to claim 11, wherein the wax is stearic acid.

14. The composition of claim 7, wherein the water soluble polymer comprises one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

15. The composition of claim 7, wherein the water insoluble polymer comprises one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

16. The composition of claim 7, wherein the alkaline metal salts of higher fatty acid comprise one or more of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

17. The composition of claim 16, wherein the alkaline metal salt of higher fatty acid is magnesium stearate.

18. The composition of claim 1, wherein the spheroid core includes one or more of pharmaceutically acceptable excipients.

19. The composition of claim 18, wherein the pharmaceutically acceptable excipients include plasticizers, diluents, colorants, and flavoring agents.

20. The composition of claim 1, wherein the enteric coating layer comprises one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid, and mixtures thereof.

21. The composition of claim 20, wherein the enteric coating includes one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

22. The composition of claim 1, wherein the composition comprises capsules, sachets, and tablets.

23. A process for the preparation of a controlled release pharmaceutical composition of tamsulosin, the process comprising:

(a) granulating tamsulosin, spheronizing agent and one or more rate controlling polymers to obtain a granulating mixture,

(b) extruding the granulated mixture to obtain extrudates,

(c) spheronizing the extrudates to obtain spherical cores,

(d) drying the spheroid cores; and

(e) coating the spheroid cores with an enteric polymer.

24. The process of claim 24, wherein the tamsulosin comprises free base, pharmaceutically acceptable salts and isomers of tamsulosin.

25. The process of claim 24, wherein the pharmaceutically acceptable salts of tamsulosin comprise hydrochloride, hydroiodide, hydrobromide, and hydrogen fumarate.

26. The process of claim 25, wherein the pharmaceutically acceptable salt of tamsulosin is a hydrochloride.

27. The process of claim 23, wherein the pharmaceutical composition comprises a concentration of about 0.03% to about 0.33% by weight of tamsulosin.

28. The process according to claim 23, wherein the spheronizing agent is microcrystalline cellulose.

29. The process of claim 23, wherein the rate controlling polymer comprises one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof.

30. The process of claim 23, wherein the pharmaceutical composition comprises a concentration of about 20% to about 90% by weight of rate controlling polymers.

31. The process of claim 29, wherein the enteric polymer comprises one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid and ethyl acrylate copolymer.

32. The process of claim 31, wherein the enteric polymer comprises one or more of methacrylic acid and ethyl acrylate copolymer.

33. The process of claim 29, wherein the wax comprises one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof.

34. The process of claim 33, wherein the wax is glyceryl monostearate.

35. The process of claim 33, wherein the wax is stearic acid.

36. The process of claim 29, wherein the water soluble polymer comprises one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

37. The process of claim 29, wherein the water insoluble polymer comprises one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

38. The process of claim 29, wherein the alkaline metal salts of higher fatty acids comprise one or more of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

39. The process of claim 38, wherein the alkaline metal salt of higher fatty acid is magnesium stearate.

40. The process of claim 23, wherein the spheroid core includes one or more of pharmaceutically acceptable excipients

41. The process of claim 40, wherein the pharmaceutically acceptable excipient comprises one or more of plasticizers, diluents, colorants or flavoring agents.

42. The process of claim 23, wherein the enteric coating comprises enteric polymers.

43. The process of claim 42, wherein the enteric polymer comprises one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid, and mixtures thereof.

44. The process of claim 42, wherein the enteric coating comprises one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

45. The process of claim 23, wherein the composition is filled into capsules, sachets, or compressed into tablets.

46. A process for the preparation of a controlled release pharmaceutical composition of tamsulosin, the process comprising:

(a) granulating tamsulosin and spheronizing agent with dispersion of one or more of rate controlling polymers to obtain granulates,

(b) extruding the granulates to form extrudates using extruder,

(c) spheronizing the extrudates until spherical cores are formed; and

(d) coating the spherical cores with an enteric polymer.

47. The process of claim 46, wherein the tamsulosin comprises free base, pharmaceutically acceptable salts and isomers of tamsulosin.

48. The process of claim 47, wherein the pharmaceutically acceptable salts of tamsulosin comprise hydrochloride, hydroiodide, hydrobromide, and hydrogen fumarate.

49. The process of claim 48, wherein the pharmaceutically acceptable salt of tamsulosin is a hydrochloride.

50. The process of claim 46, wherein the pharmaceutical composition comprises a concentration of about 0.03% to about 0.33% by weight of tamsulosin.

51. The process of claim 46, wherein the spheronizing agent is microcrystalline cellulose.

52. The process of claim 46, wherein the rate controlling polymer comprises one or more of enteric polymers, water insoluble polymers, water-soluble polymers, alkaline metal salts of a higher fatty acid, waxes, and mixtures thereof.

53. The process of claim 46, wherein the pharmaceutical composition comprises a concentration of about 20% to about 90% by weight of rate controlling polymers.

54. The process of claim 52, wherein the enteric polymer comprises one or more of hydroxylpropylmethyl cellulose phthalate, cellulose acetate phthalate, methacrylic acid and ethyl acrylate copolymer.

55. The process of claim 54, wherein the enteric polymer comprises one or more of methacrylic acid and ethyl acrylate copolymer.

56. The process of claim 52, wherein the wax comprises one or more of hydrogenated vegetable oils, esters of long chain fatty acids, long chain fatty acids, and mixtures thereof.

57. The process of claim 56, wherein the wax is glyceryl monostearate.

58. The process of claim 56, wherein the wax is stearic acid.

59. The process of claim 52, wherein the water soluble polymer comprises one or more of polyvinylpyrrolidone, hydroxypropyl cellulose, carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and mixtures thereof.

60. The process of claim 52, wherein the water insoluble polymer comprises one or more of ethyl cellulose, cellulose acetate, methacrylic acid-acrylic acid copolymers with quaternary ammonium groups, and mixtures thereof.

61. The process of claim 52, wherein the alkaline metal salts of higher fatty acids comprise one or more of magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof.

62. The process of claim 61, wherein the alkaline metal salt of higher fatty acid is magnesium stearate.

63. The process of claim 46, wherein the spheroid core includes one or more of pharmaceutically acceptable excipients

64. The process of claim 63, wherein the pharmaceutically acceptable excipient includes one or more of plasticizers, diluents, colorants, and flavoring agents.

65. The process of claim 46, wherein the enteric coating comprises enteric polymers.

66. The process of claim 65, wherein the enteric polymer comprises one or more of hydroxypropyl methylcellulose phthalate, polyvinyl phthalate, cellulose acetate phthalate, copolymers of acrylic and methacrylic acid, and mixtures thereof.

67. The process of claim 46, wherein the enteric coating comprises one or more of alkalizing agents, plasticizer, tack-modifiers and opacifiers.

68. The process of claim 46, wherein the composition is filled into capsules, sachets, or compressed into tablets.

69. A method of treating symptoms of benign prostatic hyperplasia, comprising administering a controlled-release pharmaceutical composition of tamsulosin, the composition comprising:

(a) a spheroid core comprising:

i. tamsulosin,

ii. about 10% to about 45% w/w of a spheronizing agent, and

iii. rate controlling polymers, and;

(b) an enteric coating over the spheroid core.

70. A controlled-release pharmaceutical composition comprising one or more individual units comprising:

(a) a spheroid core comprising:

i. tamsulosin,

ii. about 10% to about 45% w/w of a spheronizing agent, and

iii. rate controlling polymers, and;

(b) an enteric coating over the spheroid core.

71. The composition of claim 70, wherein the composition is filled into capsules, sachets, or compressed into tablets.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 03/06072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/18 A61K9/16 A61P13/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 064 938 A (SANOFI SYNTHELABO) 3 January 2001 (2001-01-03) claims 1-3,7-12 paragraphs '0015!-'0037! ---	1-71
Y	US 5 158 777 A (ABRAMOWITZ ROBERT ET AL) 27 October 1992 (1992-10-27) claims 1-6 column 3, line 1 -column 4, line 18 column 4, line 54 -column 4, line 68 examples 1-3 --- -/--	1-71

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2004	14/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schifferer, H

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 039530 A (LEMMENS JACOBUS M ;SYNTHON B V (NL); VAN DALEN FRANS (NL); PLATTEE) 15 May 2003 (2003-05-15) claims 1-33 page 5, line 1 -page 6, line 14 page 7, line 2 -page 9, line 12 page 10, line 3 -page 11, line 6 page 12, line 3 -page 13, line 5 page 14, line 3 -page 14, line 18 page 15, line 3 -page 18, line 17	1-4,6,7, 9,10,14, 15, 18-22, 69-71
A	DEBUNNE A ET AL: "Development and in vitro evaluation of an enteric-coated multiparticulate drug delivery system for the administration of piroxicam to dogs" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 54, no. 3, November 2002 (2002-11), pages 343-348, XP004394053 ISSN: 0939-6411 abstract page 344, left-hand column, line 45 -page 345, right-hand column, line 28	1-71
A	WILLIAMS III R O ET AL: "Influence of processing and curing conditions on beads coated with an aqueous dispersion of cellulose acetate phthalate" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 49, no. 3, 2 May 2000 (2000-05-02), pages 243-252, XP004257164 ISSN: 0939-6411 abstract page 244, right-hand column, line 6 -page 244, right-hand column, line 32	1-71
A	US 6 248 363 B1 (CHEN FENG-JING ET AL) 19 June 2001 (2001-06-19) claims 1,2,22,23,28-30,45 example 8 column 6, line 1 column 7, line 23 column 41, line 28 -column 47, line 28	1-71

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ɔnal Application No
PCT/IB 03/06072

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 1064938	A	03-01-2001	EP	1064938 A1	03-01-2001
			AU	6274700 A	31-01-2001
			BR	0011999 A	05-03-2002
			CA	2370067 A1	04-01-2001
			CN	1358088 T	10-07-2002
			CZ	20014639 A3	17-04-2002
			WO	0100182 A1	04-01-2001
			EP	1194131 A1	10-04-2002
			HU	0202259 A2	28-12-2002
			JP	2003503341 T	28-01-2003
			NO	20016282 A	27-02-2002
			PL	354399 A1	12-01-2004
			SK	19102001 A3	09-05-2002
			TR	200103604 T2	22-04-2002
			ZA	200109849 A	29-11-2002
US 5158777	A	27-10-1992	NONE		
WO 03039530	A	15-05-2003	DE	20220415 U1	09-10-2003
			WO	03039530 A1	15-05-2003
			WO	03039531 A1	15-05-2003
			NL	1021822 C2	15-07-2003
			NL	1021822 A1	08-05-2003
			NL	1021857 C2	09-01-2004
			NL	1021857 A1	08-05-2003
			US	2003147950 A1	07-08-2003
			US	2003147955 A1	07-08-2003
US 6248363	B1	19-06-2001	AU	1798101 A	04-06-2001
			CA	2391923 A1	31-05-2001
			EP	1233756 A1	28-08-2002
			JP	2003517470 T	27-05-2003
			WO	0137808 A1	31-05-2001
			US	2003077297 A1	24-04-2003
			US	2003180352 A1	25-09-2003
			US	2003215496 A1	20-11-2003
			US	2003064097 A1	03-04-2003